Original Article

Acute kidney injury in critically ill obstetric patients: Incidence and role of neutrophil gelatinase-associated lipocalcin – A prospective observational cohort study

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ABSTRACT

Background and Aims: Data focussing on acute kidney injury (AKI) in obstetric patients admitted to the intensive care unit (ICU) are scarce and even more so regarding the role of neutrophil gelatinase-associated lipocalcin (NGAL) in detecting AKI or predicting outcomes in these patients. Hence, we aim to evaluate the incidence of AKI in obstetric ICU patients and validate the role of urinary and serum NGAL in predicting the onset of AKI and mortality. **Methods:** This prospective observational cohort included 45 obstetric patients admitted in ICU, excluding those with prior renal dysfunction. Serum creatinine and urine output were monitored for the occurrence of AKI during the ICU stay. The outcome of the patient (survival or death) in the ICU and hospital was recorded, and serum and urinary NGAL were determined at the time of ICU admission. **Results:** AKI occurred in 32 [71.1%; 95% confidence interval (CI): 55.4%, 86.8%] patients during their ICU stay. Serum NGAL showed an area under receiver operating characteristic curve (AUROCC) of 0.630 (95% CI: 0.417, 0.842) ($P = 0.231$) for AKI and 0.486 (95% CI: 0.295, 0.676) ($P = 0.883$) for ICU mortality. Urinary NGAL showed AUROC = 0.472 (95% CI: 0.285, 0.660) ($P = 0.772$) to predict AKI and 0.430 (95% CI: 0.268, 0.652) ($P = 0.684$) for ICU mortality. **Conclusions:** AKI is common amongst critically ill obstetric ICU patients. However, serum and urinary NGAL cannot be advocated to discriminate between patients with or without AKI or between survivors and non-survivors in critically ill obstetric patients.

Keywords: Acute kidney injury, creatinine, critical illness, incidence, intensive care units, neutrophil gelatinase-associated lipocalcin, NGAL, obstetric, pregnancy

INTRODUCTION

Acute kidney injury (AKI) is a common morbidity affecting critically ill patients.[1] Its occurrence is associated with increased mortality and long-term renal failure.[1] In developing countries although obstetric patients frequently require intensive care unit (ICU) admission, there are only scanty data focussing on AKI.[2-4]

One of the reasons for poor outcomes in AKI is explained by delayed and imprecise identification of early AKI when using conventional diagnostic criteria consisting of serum creatinine level and urine output. Consequently, several plasma and urinary biomarkers for predicting renal injury or dysfunction early have been the subject of intense research. One of the most common biomarkers is neutrophil gelatinase-associated lipocalcin (NGAL) level in urine and serum, and it has been validated for detecting AKI since it is released within 6 hours of renal injury.[5] We

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could, however, locate only one study evaluating the role of NGAL in predicting AKI in critically ill obstetric patients.[3] Herein, only the urinary and not serum levels of NGAL were assessed. Another potential use of biomarkers for predicting AKI could be their role in predicting outcomes in the ICU for critically ill patients. Prediction of outcomes in critically ill patients may help prioritise care, make triage decisions, and allocate resources in a resource-constraint situation.

The primary objective of the present prospective cohort study was to evaluate the incidence of AKI in critically ill obstetric patients admitted to adult multi-disciplinary ICU. The secondary objectives were to assess the use of urinary and serum NGAL measured at the time of ICU admission for predicting the occurrence of AKI and mortality.

METHODS

This prospective observational cohort study was undertaken after approval from the Institutional Ethics Committee-Human Research (vide approval number IECHR/2020/PG/47/15-R1 dated 19/12/2020) and was carried out by the principles of the Declaration of Helsinki, 2013. Written informed consent was obtained from the patient or next of kin for participation in the study, and the patient's data were used for research and educational purposes. The duration of the study was from January 2021 to August 2022, and it was registered prospectively with the Clinical Trials Registry-India (vide registration number CTRI/2021/01/030557, accessible at www.ctri.nic.in/).

Obstetric patients, pre-delivery or up to 6 weeks post-delivery, admitted to ICU for any cause related directly or indirectly to pregnancy with an anticipated stay of greater than 24 hours were included. In the case of multiple admissions for the same patient, only the initial one was considered to avoid bias. If the patient was re-admitted within 24 hours after initial discharge, re-admission was considered part of initial index admission. Those not requiring insertion of a Foley's catheter, with prior history of renal dysfunction, or with requirement of renal replacement therapy or renal transplant were excluded from the study.

The occurrence of AKI and its severity was defined as per the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI[6] using changes in serum creatinine and/or urine output. All included patients were assessed for the occurrence of AKI and its severity during the entire ICU stay or truncated at seven days for longer durations. Serum creatinine was assessed at the time of ICU admission and then daily, while urine output was monitored every hour for the entire ICU stay. For the diagnosis of AKI occurring within the first 48 hours of ICU stay using serum creatinine as a marker, a comparison with the pre-admission baseline value was made. If unavailable, a baseline serum creatinine value was estimated at ICU admission using the Modification of Diet in Renal Disease (MDRD) equation. The MDRD equation assumes a lower limit of normal baseline glomerular filtration rate (GFR) of 75 ml/min/1.73 m^2. Herein, GFR = exp [5.228-1.154 × ln (S. Cr.)] × ln (age)-(0.299 if female) + (0.192 if black). AKI was managed as per existing clinical practice, and the nephrologist decided to institute renal replacement therapy.

The outcome of the patient (survival or death) in the ICU and hospital was recorded.

Blood samples (2 ml venous blood) and urinary samples were collected for NGAL determination at the earliest possible time of ICU admission. These were centrifuged and frozen at -80° C till assayed using an Enzyme-Linked Immunosorbent Assay (ELISA) kit as per manufacturer instructions (Bio vendor, Czech Republic, Czechia; Europe). The sensitivity for detection was 0.02 ng/ml. The urinary sample was taken in a sterile container directly from the catheter, not the collection bag.

The primary outcome measure was AKI in critically ill obstetric patients admitted in ICU. The secondary outcomes included serum and urinary NGAL levels and mortality. Ancillary observations noted were demographic and obstetric characteristics, need for mechanical ventilation, duration of ICU stay, and the presence or absence of certain apriori risk factors associated with AKI, including sepsis, shock, preeclampsia, maternal haemorrhage, HELLP syndrome, anaemia, disseminated intravascular coagulation (DIC) trauma, acute fatty liver, radiocontrast agents, diabetes mellitus, and nephrotoxic drugs.[6]

Considering the earlier reported incidence of AKI in critically ill obstetric patients (61%),[2] 45 patients were required at the value of 5% to detect AKI with an absolute precision of 15% on either side. Patients were included in the study as per a convenience sample based on the availability of the researcher.

Statistical Package for the Social Sciences (SPSS) version 28.0.0 (IBM SPSS statistics; Armonk, New York) was used for the statistical analysis. The Kolmogorov–Smirnov test was used to check for the normal distribution of data. Normally distributed quantitative data such as age and period of gestation were reported as mean [standard deviation (SD)], and non-normally distributed data, that is, parity, duration of presenting illness, ICU stay, hospital stay, and urinary and serum NGAL, were reported as median with interquartile ranges. Categorical data, including the reasons for ICU admission (eclampsia, severe preeclampsia, maternal haemorrhage, puerperal sepsis, uterine rupture, seizure disorder, uncontrolled diabetes mellitus, Guillain-Barre syndrome, pneumonitis), need for mechanical ventilation, in-hospital mortality, ICU mortality, incidence, and severity of AKI, were expressed as number (proportion) or percentage. A comparison of data between patients with and without AKI, such as the duration of ICU and hospital stay, in-hospital and ICU mortality, urinary and serum NGAL, and various risk factors associated with AKI, was made using the Mann–Whitney test or Chi-square test for analysing the role of serum and urinary NGAL to predict AKI and mortality, and a receiver operating characteristics (ROC) curve analysis was performed. A *P* value <0.05 was considered statistically significant.

RESULTS

One hundred four obstetric patients were admitted to the ICU during the study period (i.e., January 2021 to August 2022). Data from 45 were analysed and chosen based on the availability of the researcher during scheduled rotational postings over the entire study duration [Figure 1]. Analysis for serum/urinary NGAL was done for 39/45 patients due to a shortage of ELISA kits. The first 45 patients who fulfilled the enrolment criteria were included.

Patient characteristics and relevant obstetric details are depicted in Table 1. Pre-existing comorbidity present before the current illness included hypertension (n = 2), seizure disorder (n = 2), psychiatric disorder (n = 2), and hypothyroidism (n = 1).

The commonest reason for admission to ICU was eclampsia/preeclampsia (29/45 = 64.4%), followed by maternal haemorrhage (8/45 = 17.7%), puerperal sepsis (2/45 = 4.4%), and severe anaemia with heart failure, uterine rupture, seizure disorder, uncontrolled diabetes mellitus, Guillain-Barre syndrome, and COVID 19 pneumonitis seen in 1/45 (2.2%) each.

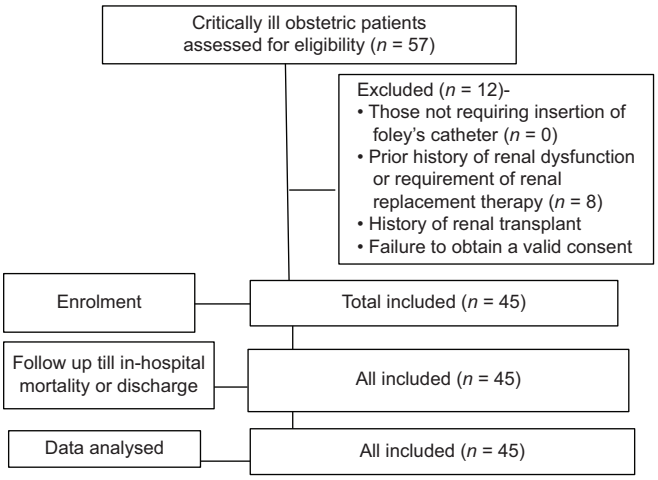

Figure 1: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flow chart. *n*=number of patients

The ICU and in-hospital mortality rates were the same (37.8%; 95% confidence interval [CI]: 1.3, 103.4). AKI developed in 32/45 (71.1%; 95% CI: 55.4%, 86.8%) patients as per KDIGO criteria. Amongst those with AKI, 8/32 (25%) had serum creatinine >1.2 mg/dl, evidenced in the referring location just before ICU admission. Severity distribution of AKI showed stages 1, 2, and 3 of the disease in 40% (n = 18), 13.3% (n = 6), and 7.8% (n = 8), respectively, and renal replacement therapy was needed in 8.9% (n = 4).

The ICU/in-hospital mortality was significantly higher in those with AKI [50% versus 7.7%, odds ratio (OR): 12; 95% CI: 1.3, 103.4] (*P* = 0.008) [Table 2]. There was no significant difference in ICU or hospital stay duration, need for mechanical ventilation, and NGAL levels [Table 2].

Serum NGAL showed an area under the ROC curve of 0.630 (95% CI: 0.417, 0.842) (*P* = 0.231) to predict AKI [Figure 2] and an area under the ROC curve of 0.486 (95% CI: 0.295, 0.676) (*P* = 0.883) for ICU mortality [Figure 3]. The use of urinary NGAL to predict AKI showed an area under the ROC curve of 0.472 (95% CI: 0.285, 0.660) (*P* = 0.772) [Figure 2] and an area under the ROC curve of 0.430 (95% CI: 0.268, 0.652) (*P* = 0.684) [Figure 3] for ICU mortality. Since the occurrence of ICU and in-hospital mortality was the same (37.8%), a separate ROC analysis was not done.

The incidence of various risk factors known to be

associated with AKI were identified for patients with and without AKI [Table 3]. Only sepsis showed a significantly greater presence in those with AKI. The use of radiocontrast dyes in 2/45 patients was done during diagnostic computed tomographic (CT) scans of the chest and head, respectively. The nephrotoxic drugs used in 41/45 patients included common antibiotics.

DISCUSSION

The incidence of AKI in critically ill obstetric patients was noted to be 71.1% in our study.

Obstetric patients may require admission to the ICU frequently, and AKI may be reported in these patients due to causes related or unrelated to pregnancy.[7] Considering stage 1 to be the mildest form of AKI and stage 3 the most severe, 40% of patients with AKI had a mild manifestation and 7.8% the most severe. There are few previously published studies exploring AKI in critically ill obstetric patients.[2-4] The earlier Indian data show greater incidences (61%, 48.1%), also approximating our present observation. The probable reason for the greater incidence could be using KDIGO rather than Risk Injury Failure Loss and End stage renal disease (RIFLE) criteria criteria in Indian studies. The KDIGO criteria consider stage 1 AKI as even a small increase in serum creatinine of ≥0.3 mg/dl in a 48-hour period, which is not included in the initial stage of the RIFLE criteria. This is corroborated by 40% of our patients with AKI to be in stage 1 of the disease. If we were to consider only stage 2 and 3 patients, the resultant incidence would decrease to 31.1%. We noted that 7.8% of patients with AKI have stage 3 of the disease, similar to earlier data.[3]

We observed a mortality of 50% in patients with AKI as compared to 7.7% in those without AKI. AKI contributing to increased mortality is well established previously.[6] The mortality rate amongst critically ill obstetric patients with AKI noted by us is higher than those reported previously.[2-4] This could be because several of our patients with AKI were suffering from eclampsia with neurological complications, and the majority were not booked for any antenatal care.[8]

In our study, neither serum nor urinary levels of NGAL were able to discriminate between patients with/without AKI or between survivors/non-survivors. Previous data have noted a similar lack of urinary and serum NGAL in separate studies for discriminating

Table 1: Patient characteristics and obstetric details

Characteristic	Value (*n*=45)
Age (years)	27.4 (5.4)
Parity	1 [1-2]
Pregnant at the time of ICU admission	5 (11.1)
Period of gestation (weeks)	35.2 (4.6)
Antenatal care provided	17 (37.8%)
Presence of pre-existing co-morbidity	7 (15.6%)
Duration of presenting illness at home, before hospitalisation (days)	1 [1-3] (0-7)

Data expressed as mean (standard deviation), median [interquartile range] (range) or number of patients (% of total number of patients); ICU=Intensive care unit, *n*=Number of patients

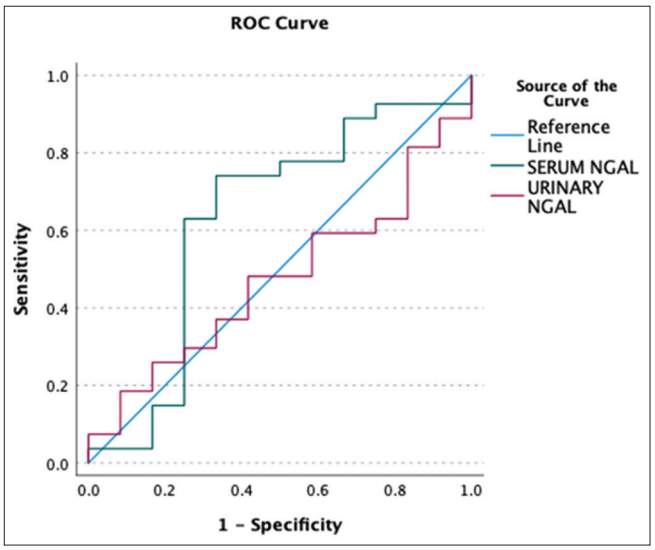

Figure 2: ROC curve for serum and urinary NGAL to predict Acute Kidney Injury. ROC= Receiver Operating Characteristics, NGAL = neutrophil gelatinase-associated lipocalcin

Table 2: Comparison of outcomes and NGAL levels in patients with and without AKI

Characteristic	Overall (*n*=45)	AKI (*n*=32)	Non-AKI (*n*=13)	Effect size (95% CI)	*P*
Duration of ICU stay (days)	5 [3-6.5] (3-43)	5 [4–7] (3-43)	3 [4–5] (3-34)	2.5 (1.6, 3.2)	0.149
Duration of hospital stay (days)	8 [6-11] (3-51)	8 [6–11] (3-51)	8 [7–11] (6-35)	0.0 (-0.6, 0.6)	0.497
ICU mortality	17 (37.8%)	16 (50%)	1 (7.7%)	12.0 (1.3, 103.4)	0.008
In-hospital mortality	17 (37.8%)	16 (50%)	1 (7.7%)	12.0 (1.3, 103.4)	0.008
Need for mechanical ventilation	43 (95.6%)	30 (93.8%)	13 (100%)	–	>0.999
Urinary NGAL (ng/ml)	4.3 [0.8-5.9]	4.2 [0.3-5.9]	4.3 [1.7-5.8]	0.1 (-0.7, 0.5)	0.784
Serum NGAL (ng/ml)	6.1 [5.4-6.4]	6.2 [5.6–6.4]	5.6 [3.4–6.3]	1.2 (0.4, 1.8)	0.201

Data expressed as median [interquartile range] (range) or number of patients (% of total patient); NGAL=neutrophil gelatinase-associated lipocalcin, AKI=acute kidney injury, ICU=Intensive care unit, *n*=Number of patients, CI=Confidence interval. *Comparison between patients with and without AKI

Table 3: Risk factors in patients with and without AKI

Characteristic	AKI (*n*=32)	Non-AKI (*n*=13)	OR (95% CI)	*P*
Sepsis	17 (53.1%)	1 (7.7%)	13.6 (1.5, 117.3)	0.004
Shock	15 (46.9%)	2 (15.4%)	4.8 (0.9, 25.4)	0.050
Preeclampsia	19 (59.4%)	9 (69.2%)	0.6 (0.1, 2.5)	0.275
Maternal haemorrhage	14 (43.7%)	3 (23.1%)	2.5 (0.5, 11.2)	0.364
Pre-existing co-morbidities	5 (15.6%)	2 (15.4%)	1.0 (0.1, 6.0)	0.984
HELLP syndrome	6 (18.7%)	0 (0%)	–	0.098
Anaemia	29 (90.6%)	9 (69.2%)	4.3 (0.8, 22.9)	0.076
DIC	0 (0%)	1 (7.7%)	–	0.118
Surgery	28 (87.5%)	12 (92.3%)	0.5 (0.0, 5.7)	0.378
Trauma	1 (3.1%)	0 (0%)	–	0.530
Acute fatty liver	2 (6.2%)	0 (0%)	–	0.368
Radiocontrast agents	2 (6.2%)	0 (0%)	–	0.368
Diabetes mellitus	1 (3.1%)	0 (0%)	–	0.511
Nephrotoxic drugs	29 (90.6%)	12 (92.3%)	0.0 (0.0, 8.5)	0.861

Data expressed as number of patients (% of total number of patients); HELLP=Hemolysis, elevated liver enzymes, low platelet; DIC=Disseminated intravascular coagulopathy; AKI=Acute Kidney Injury, *n*=Number of patients, CI=Confidence interval

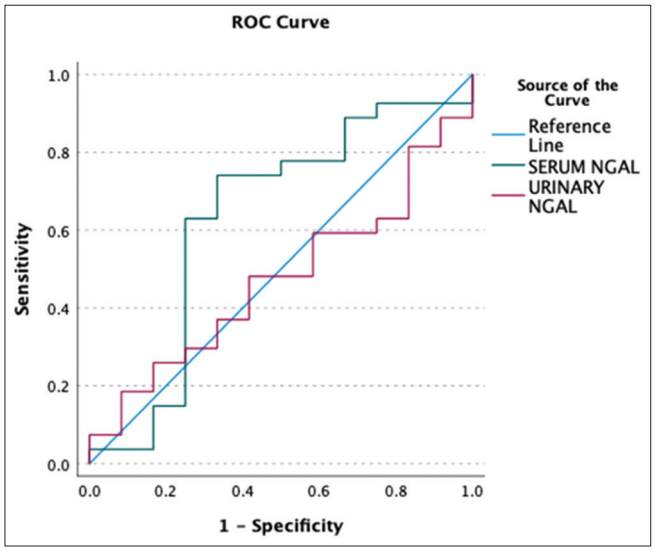

Figure 3: ROC curve for serum and urinary NGAL to predict Intensive Care Unit mortality. ROC= Receiver Operating Characteristics curve, NGAL = neutrophil gelatinase-associated lipocalcin

preeclampsia patients with and without AKI.[3,9] Another study showed that serum NGAL measured amongst preeclamptics was a successful marker of AKI.[10] However, after closer inspection, this interpretation needs to be revised. The authors compared healthy controls with preeclamptics who developed AKI; that is, there were no preeclamptics without AKI. Thus, whether the higher NGAL was a result of preeclampsia or the AKI would be difficult to conclude. A significant increase in NGAL with the rising severity of AKI, proteinuria, and creatinine that was witnessed could all be explained by the increasing severity of preeclampsia itself. The association of NGAL with the severity of preeclampsia is known, probably secondary to the inflammation and endothelial dysfunction peculiar to the disease.[2,11]

Although the present study was not designed to evaluate the causative role of various risk factors, a significantly greater incidence of sepsis was noted with AKI. There are abundant data regarding AKI in hospitalised obstetric patients for the association, though not for those within the ICU.[12,13]

The present study has certain limitations. Our study was not powered to detect the severity distribution of AKI or its relationship with the apriori risk factors. Another limitation arises from including patients without and with varying severity of preeclampsia. Since NGAL levels may depend on the increasing severity of the disease, a larger trial may help elucidate the difference in NGAL between those with and without preeclampsia.

CONCLUSION

AKI is common in critically ill obstetric patients with an incidence of 71.1%. Serum and urinary NGAL evaluated at the time of ICU admission cannot be advocated in this group of patients to discriminate between patients with or without AKI and between survivors and non-survivors.

Statement on data sharing

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

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Conflicts of interest

There are no conflicts of interest.

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